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(11) Publication number : **0 577 306 A1**

(12)

EUROPEAN PATENT APPLICATION

(21) Application number : **93304828.2**

(51) Int. Cl.⁵ : **A61K 7/16**

(22) Date of filing : **21.06.93**

(30) Priority : **22.06.92 US 901679**

(43) Date of publication of application :
05.01.94 Bulletin 94/01

(84) Designated Contracting States :
CH DE DK ES FR GB IT LI NL SE

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(54) **Oral hygiene composition.**

(57) An antiplaque mouth rinse conducive to oral hygiene. The mouth rinse composition includes a water-alcohol vehicle having dissolved therein two antibacterial agents that coact to promote the delivery of these agents and their retention on the teeth and soft tissue in the dental region of the oral cavity of the user, thereby inhibiting the formation of plaque. One agent, Triclosan, is water-insoluble and noncationic, a solubilizer therefor being included in the composition. The other agent, cetyl pyridinium chloride (CPC) is soluble in water and alcohol and is cationic. When the combination of Triclosan and CPC is delivered to the dental region, it is adsorbed and retained thereby to afford enhanced antibacterial activity.

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This invention relates generally to antiplaque mouth rinses conducive to oral hygiene, and more particularly to a mouth rinse whose formulation includes two antibacterial agents: Triclosan and cetyl pyridinium chloride. These coact to promote the delivery and retention of these agents on the teeth and soft tissue in the dental region of the oral cavity of the user to provide enhanced bacterial activity inhibiting the development of plaque.

Dental plaque is a mucous film that harbors bacteria on the teeth. Calculus or tartar is an encrustation on the teeth consisting of salivary secretions, food residues and various salts, such as calcium phosphate. Dental plaque, a precursor of calculus, unlike calculus may form on any part of the tooth surface, including the gingival margin; hence it is implicated in the occurrence of gingivitis and periodontal disease.

It is generally acknowledged in dentistry that plaque which contains a combination of pathogenic microorganisms is a principal etiological factor associated with periodontal disease, dental infections and caries. The usual approach toward combating plaque is by mechanical expedients, such as toothbrushing, dental floss and toothpicks. However, even the most thorough tooth cleaning fails to eliminate interproximal plaque, yet it is the plaque lodging between adjacent teeth that plays a major role in periodontal disease. It therefore becomes necessary to complement mechanical oral hygiene measures with chemotherapeutic agents to inhibit the development of plaque.

Among the many chemotherapeutic agents heretofore used in inhibiting dental plaque are cationic agents such as chlorhexidine. However, there are major drawbacks associated with the use of this agent; for it not only has an unpleasant taste, but it also results in staining of the teeth and tongue.

Cethyl pyridinium chloride (CPC) is another cationic agent that has been formulated into various mouth rinse products. This antiseptic is usually used in a concentration ranging from 0.05 to 0.10% in mouth rinses. Yet as noted by Moran and Addy in J. Periodontol 1991; 62:562-562, "The Effects of a Cetylpyridinium Chloride Prebrushing Rinse as an Adjunct to Oral Hygiene and Gingival Health," there seems to be general agreement that CPC mouth rinses are effective but not as effective against plaque and gingivitis as chlorhexidine, although the use of CPC does not result in significant dental staining.

Also known to be effective against plaque is Triclosan, an antibacterial agent. In the article by Gjermo and Saxton, "Antibacterial Dentifrices" appearing in J. Clin. Periodontol 1991; 18: 468-473, it is noted that several studies indicate that Triclosan alone, in spite of its broad antibacterial spectrum, has only a moderate effect on plaque formation. While Triclosan has been shown to be retained in plaque for several hours, the salivary release curve is relatively steep, thereby indicating a rapid release from oral binding

sites. On the other hand, when Triclosan is incorporated in a copolymer which is retained on oral surfaces, it then provides the oral cavity with a reservoir of Triclosan. However, the copolymer makes no contribution to combating plaque.

As indicated in the Gaffar et al. patent, 5,043,154, cationic antibacterial materials such as chlorhexidine and CPC have been the subject of many investigations as antibacterial agents. Nevertheless, in spite of the fact that these cationic agents have been used in conjunction with zinc salt acting as an anticalculus agent, they have not been found to be effective when used with anionic materials, such as a polyphosphate anticalculus agent.

In the oral composition disclosed in the Gaffar et al. patent '154, the mouth wash formulation includes a water-soluble polyphosphate salt as an anticalculus agent in combination with the water-insoluble noncationic antibacterial compound Triclosan, acting as an antiplaque agent. Triclosan is 2, 4, 4'-trichloro-2'-hydroxydiphenyl ether.

The antibacterial composition disclosed in the Nabi et al. patents 4,894,220 and 5,037,635 for use as a dentifrice or mouth wash contains water and includes Triclosan, a substantially water-insoluble noncationic antiplaque agent as well as a solubilizer therefor, such as propylene glycol. The formulation further includes a synthetic anionic linear polymeric polycarboxylate having a molecular weight of about 1000 to about 1,000,000. The anionic polymeric agent is said to enhance the delivery and retention of the antibacterial agent on teeth and on soft oral tissue. But this polymeric agent lacks antibacterial properties and does not itself act to retard the growth of plaque, even though it is retained in the dental region.

In the Gaffar et al. patent 5,037,637, there is disclosed an oral composition such as a mouth rinse containing a polyphosphate anticalculus agent and Triclosan, an antibacterial, antiplaque agent compatible therewith. The vehicle for these constituents is a water-alcohol mixture that includes a humectant. The total amount of water-alcohol in this preparation exceeds 70% by weight.

The Reed et al. patent 5,032,385 discloses an oral hygiene composition that includes Triclosan and polyethylene glycol. This patent points out that Triclosan, because of its lipophilic nature, tends to partition into a hydrophobic oil phase and a surfactant micellar phase and is therefore rendered unavailable for adsorption into the oral surfaces to be treated. By incorporating specified amounts of polyethylene glycol into the composition, the oral availability of the Triclosan can be maintained at an effective level.

In view of the foregoing, the main object of this invention is to provide an antiplaque mouth rinse whose composition includes two antibacterial agents which when used alone have limited effectiveness, but which when combined coact to promote the deliv-

ery to and the retention of these agents in the mouth and soft tissues in the dental region of the oral cavity, thereby enhancing the antibacterial activity inhibiting the development of plaque.

More specifically, an object of this invention is to provide a mouth rinse of the above type in which one of the antibacterial agents is Triclosan and the other, cetyl pyridinium chloride or another cationic antibacterial agent, which together give rise to enhanced antibacterial activity highly effective against the formation of plaque.

Also an object of this invention is to provide an antiplaque mouth rinse which is free of toxic agents and is pleasant tasting to render it acceptable to a typical user.

Briefly stated, these objects are attained in an antiplaque mouth rinse conducive to oral hygiene. The mouth rinse composition includes a water-alcohol vehicle having dissolved therein two antibacterial agents that coact to promote the delivery of these agents and their retention on the teeth and soft tissue in the dental region of the oral cavity of the user, thereby inhibiting the formation of plaque.

One agent, Triclosan, is water-insoluble and non-cationic, a solubilizer therefor being included in the composition. The other agent, cetyl pyridinium chloride (CPC) is soluble in water and alcohol and is cationic. When the combination of Triclosan and CPC is delivered to the dental region, it is adsorbed and retained thereby to afford enhanced antibacterial activity.

In an antiplaque mouth rinse in accordance with the invention, the vehicle or carrier for delivering the active antibacterial constituents to the dental region in the oral cavity of the user is a water-alcohol mixture in which the ratio of water to alcohol is about 4 to 1 by weight to about 6 to 1. The water is preferably deionized, and the alcohol, which must be non-toxic in nature, is preferably ethanol or grain alcohol, although isopropanol is also usable. Thus the amount of water by weight in the mouth rinse may be about 67% and the amount of alcohol, about 18%.

Also included in the mouth rinse composition is a humectant having an affinity for water and a stabilizing effect thereon. A preferred humectant is sorbitol in a 70% aqueous solution. The amount of sorbitol included in the formulation is preferably between about 10 to 15% by weight.

In the mouth rinse in accordance with the invention, two antibacterial agents are included, which by themselves, as indicated in the prior art, have limited effectiveness in combating the formation of plaque, but which when combined in the rinse coact to promote their delivery to and retention on the teeth and soft tissue in the dental region of the oral cavity and thereby strongly inhibit the formation of plaque.

Water-insoluble, non-cationic antibacterial agents, which are particularly desirable in terms of

antiplaque effectiveness and safety, are halogenated diphenyl ethers, preferably Triclosan. In the present mouth rinse composition, an effective amount of Triclosan is included, typically about 0.01 to 0.05% by weight, preferably 0.03%.

Triclosan is substantially water-insoluble, meaning that its solubility is less than about 1% by weight in water at 25°C. Hence the composition must include a solubilizer for the Triclosan which does not adversely affect its antibacterial activity. The amount of the solubilizer may be between about 0.5 to 2.0% by weight, and must be sufficient to solubilize the water-insoluble Triclosan. A preferred solubilizer for this purpose is TWEEN 20 manufactured by Atlas Chemical Industries, Inc. TWEEN is the trademark for polyoxyethylene derivatives of fatty acid partial esters of sorbital anhydrides that are generally soluble in water.

The second antibacterial agent included in the mouth rinse is cetyl pyridinium chloride (CPC), which is the monohydrate of the quarternary salt of pyridine and cetyl chloride. CPC, which is cationic, is highly soluble in water and alcohol. The percentage by weight of CPC in the mouth rinse is in the range of about .020 to .030%, preferably about .025%, so that the amount by weight of the antibacterial agent in the formulation is almost equal to that the Triclosan agent, which is non-cationic.

We have found that the combination of the cationic with the non-cationic antibacterial agents has two significant effects: the first being that the combined agents are readily adsorbed in the dental region and retained on the teeth and soft tissue for a relatively prolonged period and are not released by saliva in the oral cavity.

The second effect is that these agents coact to afford enhanced antibacterial activity that is highly effective against plaque, particularly interproximal plaque that is not reachable by mechanical expedients.

Also included in the composition is a defoaming agent, such as Pluronic L64 manufactured by Wyandotte Chemicals Corporation, preferably in an amount of about 10% by weight. Pluronic is the trademark for polyoxyalkylene derivatives of propylene glycol.

A small amount of sodium saccharine, say, about 0.75% by weight, may be added to the mouth rinse. This sweetener is highly soluble in water and is many times sweeter than sugar, thereby imparting a pleasant taste to the mouth rinse.

The mouth rinse may also include an effective amount of an anti-caries agent soluble in water, such as sodium fluoride, which is compatible with the antibacterial agents. And also included in small amounts, about 0.1% by weight, are coloring agents such as FD&C BLUE #1 and FD&C YELLOW #5.

The selected cationic and non-cationic antibacterial agents are compatible with each other and together provide enhanced bacterial activity when de-

livered to and adsorbed by the dental region of the oral cavity of the user where they function to combat the formation of plaque.

While CPC is the preferred water-soluble cationic antibacterial agent and provides distinct advantages, usable in place of CPC in combination with Triclosan are such water-soluble cationic antibacterial agents as chlorhexidine and domiphen bromide, a quaternary salt.

A two-component antibacterial composition in accordance with the invention is not limited in its utility to mouth rinse procedures in which the user takes a small amount of the rinse in his mouth and swishes it around to bathe the dental region, and then spits it out, the agents being adsorbed and retained by the teeth and soft tissue.

In practice, the mouth rinse may also be used for subgingival irrigation, in which case the rinse is poured into the reservoir of a dental irrigation device, such as the well known WATER PIK device. This device ejects the rinse as a stream through a hand-held nozzle which directs the stream toward a subgingival region.

A rinse in accordance with the invention may also be used as an impregnant for filling hollow, synthetic fibers for the localized delivery of antibacterial agents to treat disease-active pockets of periodontitis.

As indicated by Morrison et al. in *Journal Periodontal*, February 1992, in an article entitled "Root Surface Characteristics Associated with Subgingival Placement of Monolithic Tetracycline-Impregnated Fibers," the use of such impregnated fibers dramatically changes the subgingival microbial flora and decreases clinical signs of inflammation. The advantage of using a two-component antibacterial agent, one non-cationic and the other, cationic, in accordance with the invention, in place of tetracycline lies in the adsorption and retention characteristics of these combined agents and their enhanced antimicrobial activity at the diseased site.

It is also now known to implant drug-impregnated polymer wafers or other matrixes in various parts of the body to deliver drugs that cannot be delivered by mouth or through the skin. The polymer used for the wafer is one that is biodegradable and acts to release the impregnant as the wafer gradually dissolves. Such wafers may be impregnated with a two-component antibacterial composition in accordance with the invention, thereby slowly releasing this composition into a site to be treated over a prolonged period.

While there have been disclosed and described preferred compositions of an antiplaque mouth rinse in accordance with the invention, it will be appreciated that many changes and modifications may be made therein without, however, departing from the essential spirit thereof. Thus the composition may be applied to a dental floss in fluid or in gel form.

Claims

1. An antibacterial mouth rinse composition comprising a water-alcohol vehicle having dissolved therein two antibacterial agents that coact to promote their delivery and retention on the teeth and soft tissue in the dental region of the oral cavity and thereby inhibit the formation of plaque, one being Triclosan, which is substantially water-insoluble and non-cationic, the other being cetyl pyridium chloride, which is cationic and soluble in water and alcohol, and a solubilizer in an amount sufficient to solubilize the Triclosan, the amount of Triclosan relative to the amount of cetyl pyridium chloride being such that together they are more effective in inhibiting the formation of plaque than either Triclosan or cetyl pyridium chloride.
2. A mouth rinse composition as set forth in claim 1, wherein said water is deionized water and said alcohol is ethanol.
3. A mouth rinse composition as set forth in claim 2, wherein the ratio of water to alcohol by weight is about 4 to 1.
4. A mouth rinse composition as set forth in claim 1, further including a sweetening agent.
5. A mouth rinse composition as set forth in claim 1, further including a humectant.
6. A mouth rinse as set forth in claim 5, wherein said humectant is sorbital.
7. A mouth rinse composition as set forth in claim 1, wherein said solubilizer is a polyoxyethylene derivative of a fatty acid partial ester of sorbital anhydrides.
8. A mouth rinse composition as set forth in claim 1, further including a defoaming agent.
9. A mouth rinse composition as set forth in claim 8, wherein said defoaming agent is a polyoxyalkylene derivate of polypropylene glycol.
10. A mouth rinse composition as set forth in claim 1, further including a small but effective amount of an anti-caries agent.
11. A mouth rinse composition as set forth in claim 1, wherein said anti-caries agent is sodium fluoride.
12. A mouth rinse composition as set forth in claim 1, further including a coloring agent.

13. A mouth rinse composition as set forth in claim 1, in which the percentage by weight of the CPC is in the range of about .020 to .030%.

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14. A mouth rinse composition set forth in claim 13, in which the percentage by weight of the Triclosan is in the range of about 0.01 to 0.05%.

15. An antibacterial composition for inhibiting the formation of plaque comprising a water-alcohol vehicle having dissolved therein two antibacterial agents that coact to promote their delivery to a site, one being Triclosan, which is substantially water-insoluble and non-cationic, the other being an antibacterial agent which is cationic and soluble in water, and a solubilizer in an amount sufficient to solubilize the Triclosan, the amount of Triclosan relative to the amount of the non-cationic agent being such that they are more effective in inhibiting the formation of plaque than either Triclosan or the non-cationic agent.

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EUROPEAN SEARCH REPORT

Application Number

EP 93 30 4828

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Y	US-A-4 205 061 (J.D. VIDRA) * claims 1-5; example I *	1-15	A61K7/16
Y	WO-A-9 208 442 (WARNER-LAMBERT) * claims 1,2; examples IV,VI *	1-15	
Y	US-A-4 022 880 (L.J. VINSON ET AL.) * column 6, line 61; claims 1,7,18-20; examples 11,26 *	1-15	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			A61K
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 14 OCTOBER 1993	Examiner WILLEKENS
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons</p> <p>& : member of the same patent family, corresponding document</p>			

EPO FORM 1503 03.82 (P0401)